REMARKS

Claims 1-6 and 8-15 are pending in this application. Claim 7 has been canceled. Claims 10-15 have been added. Support for new claims 10-15 is found in original claim 9, as well as at page 1 and in the examples described in the present specification.

Submission of Abstract

As indicated earlier in this Reply, an Abstract is being submitted in order to comply with the requirement under 37 C.F.R. § 1.72(b).

Removal of Issue under 35 U.S.C. § 101

Claim 7 has been rejected under 35 U.S.C. § 101 as being an improper "use" claim. Claim 7 has been canceled so as to remove this issue.

Issues under 35 U.S.C. § 112

Claims 7-9 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to satisfy the enablement requirement with regard to all of the diseases recited in these claims. It is noted that claim 7 has been canceled.

In response to the above-noted rejection, it is noted that the basis of this rejection rests primarily on the argument that there

is no description in the present specification or in the literature that inhibitors of cytokines, such as interleukin 1-beta and TNF-alpha, such as the compounds of the present invention, are implicated in the etiology of AIDS or osteoporosis. In response to this argument, applicants hereby submit the following evidence implicates such cytokine inhibitors in the etiology of AIDS and osteoporosis: (1) WO 95/35304 which discloses the role of TNF in the pathophysiology of AIDS (note for example page 3, lines 3-8); and (2) WO 98/52558 which discloses that TNF-alpha mediates a variety of diseases, such as osteoporosis (note page 2, line 16-23). Consequently, it is submitted that the basis for the above-noted rejection under 35 U.S.C. § 112 has been removed upon the submission of this evidence of items (1) and (2). It is further submitted that all of the presently pending claims comply with all requirements under 35 U.S.C. § 112 such that the rejection should be withdrawn.

Issues under 35 U.S.C. § 103(a)

Claims 1-9 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Ottosen '730 (WO 98/32730). This rejection is traversed for the following reasons.

Present Invention and Advantages Thereof

The present invention is directed to selected aminobenzophenone compounds of formula I which have unique structurally characteristics and advantageously unique pharmaceutical properties. The compounds of formula I of the present invention: [1] require that the substituent R_1 be in the "ortho" position, rather than any position, of the first phenyl ring of formula I; [2] require that substituent R_2 be in the "ortho" position, rather than any position, of the second phenyl ring of formula I; and [3] require that the urea group HN-CONH-Q-Y be in the 2-position, rather than any position, of the third phenyl ring of formula I. By selecting these specific chemical structural characteristics, the inventors have obtained compounds which exhibit significant pharmacological properties over compounds having similar structures. For example, the compounds of the present invention advantageously exhibit: [i] an improved biological activity *in vivo* with respect to inhibition of LPS induced TNF-alpha production in mice, and [ii] markedly increased absorption upon ip administration as described below.

Comparable *in vitro* Activity

Compounds of the invention have been tested in the *in vitro* IL-1β and TNF-α assay as well as PMN superoxide production assay

described in the present application (see page 7, line 34 - page 8, line 27). The results are shown in the table below as the median inhibitory concentration (IC_{50}, nM) of the compounds tested.

Compound	IL-1	TNF	PMN superoxide
110	5.0	5.0	2.5
108	63	13	2.5
156 of WO98/32730	13	7.1	5.0

It appears that the *in vitro* activity of the tested compounds is comparable to that of compound 156 by Ottosen '730 (erroneously indicated as reference compound 106 in Table 1 of the present application). It should be noted that compound 156 is the compound with the highest biological activity of those compounds disclosed by Ottosen '730 which have been tested.

Superior *in vivo* Activity

The compounds were also tested in an *in vivo* screening model of LPS induced TNF-α response in mice. The model was set up as follows:

Groups of 6 mice (C3H/HeN, female, about 8 weeks (20 g), Bomholtgaard) were dosed with test compounds in suspension vehicle 1 hour prior to LPS administration (LPS from *E. coli* 055:85:B5, L-4005, Sigma). At time zero, the mice were dosed ip with 1.0 mg

LPS/kg. After anesthetization with Hypnorm/Dormicum, the mice were bled from the periobital venous plexus 80-90 minutes after LPS administration. The blood samples were sampled in EDTA stabilized tubes and centrifuged at 4000 rpm for 10 minutes at 4°C. The plasma level of TNF-α was analyzed by ELISA. Compound 156 of Ottosen '730 was used as reference compound.

The plasma level of TNF-α was determined using a sandwich ELISA. Microtiter plates were coated with a monoclonal antibody against mouse TNF-α recombinant standards were added to the wells of the microtiter plates and incubated. All standards were tested in triplicate, all plasma sample in single. After sample and standard incubation, the plates were washed and incubated with biotinylated polyclonal secondary antibody against mouse TNF-α and washed. Enzyme conjugate was added to all wells and incubated. Substrate was added and the enzyme/substrate reaction stopped after 15 minutes at room temperature with 1M H^2SO_4. The colour development (OD) was measured at 450 nm on an ELISA reader and the background OD at 620 nm was subtracted.

Experiments were approved if the group treated with the reference compound showed a significant inhibition ($p<0.05$) of the TNF-α response compared to the LPS treated control group. The results of the tested compounds are indicated as a percentage inhibition compared to an LPS treated control group. Compounds

were tested at 10 mg/kg. The Mann-Witney test was used to compare drug treated groups to the LPS treated control group ($p<0.05$).

In this model, compounds 110 and 108 of the invention were found to provide a 70% and 72% inhibition, respectively, of LPS induced TNF-α production compared to a 23% inhibition provided by compound 156 of Ottosen '730.

Superior *in vivo* Absorption

The absorption of compounds of the invention was determined by administering 20 mg/kg of the test compound as a single dose ip to groups of 15 female mice (about 25 g). From samples were taken from three animals in each group at 0.5, 1, 2, 4 and 6 hours after administration. The serum levels of the test compounds were measured by HPLC. The results are given as ng/ml serum. Compound 156 of WO 98/32730 was used as reference.

Upon ip administration (10 mg/kg), compound 102 of the invention was found to have an absorption of 123 ng/ml compared to 20 ng/ml for compound 156 of Ottosen '730. Furthermore, compound 102 was absorbed at 275 ng/ml on oral administration, whereas compound 156 of Ottosen '730 is not absorbed at all on oral administration.

Distinctions between the Present Invention and Ottosen '730

Ottosen '730 discloses aminobenzophenones useful as inhibitors of interleukin and TNF of general formula (I).

Ottosen '730 fails to disclose or provide any basis for a person skilled in the art to select the above-noted structural features [1], [2] or [3] for each of the phenyl rings as discussed above which features are present in the compounds of the present invention. Further, Ottosen '730 fails to disclose or recognize the significant advantages associated with the compounds of the present invention with regard to advantageously improved activity and absorption properties as evidenced by the comparative experimental test results summarized above.

Since Ottosen '730 discloses a very large "genus" of compounds, it is submitted that the specific of the present invention are not rendered *prima facie* obvious in view of this disclosure of Ottosen '730. Note that the fact that the claimed species or subgenus is encompassed by a prior art genus fails to be sufficient by itself to establish a *prima facie* case of obviousness. In re Baird, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994); In re Jones, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992); In re Deuel, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995); MPEP 2144.08, Rev. 1 February 2003, page 2100-141. Consequently, it is submitted that Ottosen

'730 discloses such a large genus that the assertion of *prima facie* obviousness fails to be adequately supported.

In addition, the above-noted experimental comparative test results rebut any asserted *prima facie* obviousness, since the claims of the present invention exhibit unexpected advantageous and superior properties over similar compounds disclosed by Ottosen '730. Such evidence may be properly used to rebut a *prima facie* case of obviousness. In re Pabesch, 137 USPQ 43 (CCPA 1963); In re Wiechart, 152 USPQ 247 (CCPA 1967); MPEP 2144.09, Rev. 1 February 2003, pages 2100-153. Consequently, it is submitted that even if *prima facie* obviousness has been properly alleged, this has been rebutted.

In view of the above, it is submitted that the present claims patentably define over Ottosen '730 such that the above-noted rejection should be withdrawn.

It is submitted for the reasons stated above that the present application should now be placed into condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Andrew D. Meikle, #32,868

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

ADM/csm
3893-0139P

Attachment(s): Abstract
WO95/35304
WO98/52558